REMARKS

Upon entry of this amendment, claims 19-25, 27, 28, 72, and 73 will be pending in the application. Claim 19 is amended to recite the step of "introducing into an antibody-producing mammalian cell a polynucleotide that disrupts the function of a gene encoding alpha-1-antitrypsin, a polynucleotide that disrupts the function of a gene encoding endothelial monocyte activating polypeptide I, or both, wherein the cell expresses a higher titer of an antibody as compared with identical cells into which said polynucleotide that disrupts the function of a gene encoding alpha-1-antitrypsin, said polynucleotide that disrupts the function of a gene encoding endothelial monocyte activating polypeptide I, or both has not been introduced." Exemplary support for the amendment of claim 19 is located in claim 28 and throughout the specification. Claims 27 and 28 are amended to be consistent with the amendment to claim 19. New claim 73 recites the method of claim 19 wherein the alpha-1-antitrypsin comprises an amino acid sequence of SEQ ID NO:21, 22, 23, 24, 25, 26, or 27 and the endothelial monocyte activating polypeptide I comprises an amino acid sequence of SEQ ID NO: 28, 29, 30, 31, 32, 33, or 34. Exemplary support for claim 73 is located in paragraph 0036 of the specification. Claims 21-25 are withdrawn. Claims 1-18, 26, and 29-71 are canceled. No new matter is added.

As an initial matter, Applicants note that the copies of the Supplemental Information Disclosure Statement submitted April 18, 2007 attached to the Office Action of August 29, 2007 were signed but not initialed to indicate consideration by the Office. Initialed copies of the Supplemental Information Disclosure Statement submitted April 18, 2007 are requested. Consideration of the Supplemental Information Disclosure Statement submitted November 14, 2007 also is requested.

The claims are fully enabled by the present specification.

Claims 19, 20, 28, and 72 are rejected under the first paragraph of 35 U.S.C. § 112 for alleged lack of enablement. Without conceding the propriety of the rejection, Applicants amend herein claim 19 to recite "[a] method for producing a high titer antibody producing cell *in vitro* comprising introducing into an antibody-producing mammalian cell a polynucleotide that disrupts the function of a gene encoding alpha-1-antitrypsin, a

polynucleotide that disrupts the function of a gene encoding endothelial monocyte activating polypeptide I, or both, wherein the cell expresses a higher titer of an antibody as compared with identical cells into which said polynucleotide that disrupts the function of a gene encoding alpha-1-antitrypsin, said polynucleotide that disrupts the function of a gene encoding endothelial monocyte activating polypeptide I, or both has not been introduced." Applicants traverse the rejection to the extent it is applied to the amended claims.

In making a determination of enablement, the inquiry is not whether experimentation is required, but rather whether the experimentation required is undue. According to the Federal Circuit, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed . . . ." *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988) (citations omitted). In *In re Wands*, eight factors to be considered in assessing whether a disclosure is enabling were elucidated: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, a patent claim is invalid for lack of enablement in instances in which consideration of the *Wands* factors leads to a conclusion that practice of the invention would require undue experimentation.

The nature of the invention; the breadth of the claims

Applicants amend herein claim 19 to recite "[a] method for producing a high titer antibody producing cell *in vitro* comprising introducing into an antibody-producing mammalian cell a polynucleotide that disrupts the function of a gene encoding alpha-1-antitrypsin, a polynucleotide that disrupts the function of a gene encoding endothelial monocyte activating polypeptide I, or both, wherein the cell expresses a higher titer of an antibody as compared with identical cells into which said polynucleotide that disrupts the function of a gene encoding alpha-1-antitrypsin, said polynucleotide that disrupts the function of a gene encoding endothelial monocyte activating polypeptide I, or both has not been introduced." The breadth of the claims is thus consistent with the enabling disclosure of the

specification and the examples provided therein in view of the knowledge and level of skill in the art.

The level of skill of those in the art; the state of the art

The present claims recite "introducing into an antibody-producing mammalian cell a polynucleotide that disrupts the function of a gene encoding alpha-1-antitrypsin, a polynucleotide that disrupts the function of a gene encoding endothelial monocyte activating polypeptide I, or both, wherein the cell expresses a higher titer of an antibody as compared with identical cells into which said polynucleotide that disrupts the function of a gene encoding alpha-1-antitrypsin, said polynucleotide that disrupts the function of a gene encoding endothelial monocyte activating polypeptide I, or both has not been introduced." The elected species under examination is a knock-out targeting vector. The Office states that "complete removal of the alpha-1-antitrypsin (AAT) gene(s) in any organism for the production of high-titer antibody producing cells … is not a routine practice." Office Action, page 7. To the extent this ground for rejection is applied to the presently amended claims, Applicants disagree.

The state of the art of gene knockout technology was highly developed and the level of those of skill in the art was quite high as of the priority date of the present application. As set forth in the previously submitted Declaration of J. Bradford Kline, Ph.D. Pursuant to 37 CFR § 1.132 ("Kline Declaration"), thousands of articles and numerous books described gene knockout methods and provided detailed protocols for performing those methods. See Kline Declaration, paragraphs 6-8. Moreover, gene knockout technology was so advanced and routine that it was regularly taught and practiced in the laboratory portion of college biology courses. See Kline Declaration, paragraph 12.

Once Applicants identified the significance of suppression of expression of the alpha-1-antitrypsin and endothelial monocyte activating polypeptide I genes on antibody production, it required no more than routine experimentation on the part of the ordinarily skilled artisan to develop polynucleotides for introduction into antibody-producing mammalian cells to enhance antibody production in accordance with the claimed methods. As explained by Dr. Kline, AAT and EMAP genes from species including human, mouse, chimp, and rat were known and publicly available as of the filing date of the present

application. See Kline Declaration, paragraph 11. Generation of targeting vectors and introduction thereof into antibody-producing mammalian cells was well within the skill of the ordinarily skilled artisan at the time of filing. See Kline Declaration, paragraphs 12-20. Moreover, one of ordinary skill in the art would have been able to readily identify cells that exhibit enhanced antibody production based on the knowledge in the art and the guidance of the specification. See, e.g., Example 3 of the specification.

It would have required no more than routine experimentation on the part of the ordinarily skilled artisan to design one or more knock-out targeting vectors directed to the alpha-1-antitrypsin and endothelial monocyte activating polypeptide I genes and to introduce the vector(s) in an antibody-producing mammalian cell to suppress gene expression in accordance with the claims in view of the knowledge and skill in the art and the detailed teachings of the present specification.

The amount of direction or guidance presented; the presence or absence of working examples; the quantity of experimentation necessary; the predictability or unpredictability of the art

One skilled in the art, armed with the detailed teachings of the present specification and the examples provided therein, would have been able to make and use the presently claimed invention with no more than routine experimentation. The specification provides detailed guidance for disrupting the function of a gene encoding alpha-1-antitrypsin, for disrupting the function of a gene endothelial monocyte activating polypeptide I, or for disrupting both, to enhance antibody production by a cell in accordance with the claimed methods. See Examples 3 and 5 of the specification; see also Kline Declaration, paragraph 29, Exhibit D.

In support of its conclusion of nonenablement, the Office first asserts that "the specification does not provide specific active steps to guide an artisan to effectively inactivate all mammalian AAT genes by homologous recombination with one knock-out targeting vector." Office Action, page 5. The claimed methods, however, do not require inactivation of "all mammalian AAT genes." Rather, the claims recite "introducing into an antibody-producing mammalian cell a polynucleotide that disrupts the function of a gene encoding alpha-1-antitrypsin, a polynucleotide that disrupts the function of a gene encoding endothelial

monocyte activating polypeptide I, or both, wherein the cell expresses a higher titer of an antibody as compared with identical cells into which said polynucleotide that disrupts the function of a gene encoding alpha-1-antitrypsin, said polynucleotide that disrupts the function of a gene encoding endothelial monocyte activating polypeptide I, or both has not been introduced."

The Office further asserts that an unsupported functional redundancy among members of the AAT and EMAPI gene families undermines the predictability of the claimed methods and that "despite the general high level of expertise in the art, considerable unpredictability exists in the field regarding any effect AAT has on antibody production and secretion." Office Action, pages 7-8. Applicants strongly disagree. No basis for concluding that various AAT genes are functionally redundant other than structural homology has been asserted by the Office. Office Action, page 7. As noted by the Forsyth reference upon which the Office relies, however, the SERPIN family to which the AAT genes belong are *functionally diverse*. Forsyth *et al.*, *Genomics*, 81:336-345 (2003). Regarding the alleged functional redundancy of the EMAPI genes, a mere statement by the Office that "it would not be surprising if the two polypeptides are functionally equivalent" based on structural homology (Office Action, page 8) does not constitute evidence for purpose of making an enablement rejection. Similarly, the statement that functional redundancy is "a realistic possibility" (Office Action, page 11) does not carry the Office's burden in establishing a *prima facie* case of nonenablement. The Office is invited to submit a declaration to that effect if it so desires. Additionally, in response to the assertion that similar EMAPI genes are functionally equivalent because no obvious phenotypes were displayed by mice null for the murine calgizzarin like gene, it is noted that the phenotypic analysis conducted by Mannan *et al.* (*Mol. Repro. Dev.*, 66:431-438 (2003)) focused on gross abnormalities in testis morphology, spermatogenesis, and fertility. There is no evidence on the present record that antibody production by those mice was considered. Accordingly, no basis upon which it can be concluded that structurally similar EMAP genes are functionally redundant has been established.

The Office asserts on pages 9-10 of the Office Action that phenotypes associated with *in vivo* gene targeting cannot be predicted on the basis of *in vitro* gene targeting studies. Without conceding the propriety of the assertion, Applicants note that the Office's assertions

regarding the unpredictability of determining the phenotype conferred by knock-out technology conducted *in vivo* based on *in vitro* studies are irrelevant to the enablement analysis of the present claims which recite *in vitro* methods.

Moreover, the Office seems to have overlooked the evidence presented in the present specification in support of the effect of suppression of expression of the alpha-1-antitrypsin and endothelial monocyte activating polypeptide I genes on antibody production by a mammalian cell. Example 1 of the specification describes the H6 cell line as a murine hybridoma cell line producing antibodies against IgE protein. Example 2 of the specification describes the H34 cell line derived from the parental H6 line that exhibits enhanced antibody production. Differential microarray analysis of steady state transcripts of the two cell lines revealed suppressed expression of the alpha-1-antitrypsin and endothelial monocyte activating polypeptide I genes. See specification, Example 3. Applicants demonstrated that expression of antisense AAT and EMAPI vectors in the H6 parental line enhanced antibody production. Conversely, expression of sense AAT and EMAPI vectors in the H34 cell line suppressed antibody production. See specification, paragraphs 0073 and 0074, Table 2. One skilled in the art would thus not expect modulation of expression of "all mammalian AAT genes" or of all endothelial monocyte activating polypeptide I genes to be required to affect antibody production.

Indeed, as explained by Dr. Kline, one skilled in the art would expect enhanced antibody production upon suppression of expression of the gene encoding alpha-1-antitrypsin, endothelial monocyte activating polypeptide I, or both in an antibody-producing mammalian cell. As an initial matter, AAT and EMAP knockout would not be expected to be lethal. See, Kline Declaration, paragraph 27. Indeed, mice null for the murine calgizzarin like gene were viable (Mannan *et al.*, *Mol. Repro. Dev.*, 66:431-438 (2003)). Additionally, an antisense-knockdown phenotype generally correlates with its respective knockout phenotype. See Kline Declaration, paragraph 28. Thus, those of skill in the art would have reasonably expected that the AAT and EMAP antisense phenotypes would also be observed in cells in which these genes have been knocked out. Dr. Kline further explained that any relevant secondary phenotypical changes occurring with gene knockout would be expected to also be present in antisense studies. Kline Declaration, paragraph 33. Identification of the exact mechanism by which the presently claimed methods enhance antibody production is not

required for enablement. Applicants need only teach how to make and use the claimed invention without undue experimentation, a standard that has been clearly met.

One skilled in the art would be able to predictably reproduce the methods for producing a high titer antibody producing cell *in vitro* demonstrated by the Applicants with no more than routine experimentation in view of the guidance provided by the specification and the knowledge and skill in the art. Withdrawal of the rejection is thus respectfully requested.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Respectfully submitted,

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